

## DOCKET NO.: ISIS0171-100 (ISPH-0794)

## PATENT

## In the Claims:

The current status of all claims is listed below and supercedes all previous lists of claims.

Please cancel claims 10, 12-16, 23, 24, 30, and 31 without prejudice to their presentation in another application, and amend claims 1-3, 9, 11, and 17-22 as follows:

1. (currently amended) A method of identifying an oligonucleotide sequence ~~motifs~~ motif which ~~are~~ is correlated with antisense oligonucleotide activity comprising:

~~a. providing a set of antisense oligonucleotide sequences, each of which has an experimentally determined capacity to inhibit expression of its complementary nucleic acid target;~~

~~b. subdividing each of said antisense oligonucleotide sequences~~ sequence of a set of antisense oligonucleotide sequences into subsequences of defined length, each unique subsequence being a motif, wherein each of the antisense oligonucleotide sequences has an experimentally determined capacity to inhibit expression of its complementary nucleic acid target;

~~c. determining which motifs significantly correlate with antisense oligonucleotide activity; and~~

~~d. eliminating the motifs whose correlation with antisense oligonucleotide activity is unique to a particular nucleic acid target.~~

2. (currently amended) The method of claim 1 wherein the defined length of the ~~motifs~~ motif is from two to ten nucleotides in length.

3. (currently amended) The method of claim 2 wherein the defined length of the ~~motifs~~ motif is from three to four nucleotides in length.

4. (original) The method of claim 1 wherein determining which motifs significantly correlate with antisense oligonucleotide activity is done by T-test.

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5. (original) The method of claim 1 further comprising relating the probability of antisense oligonucleotide activity to the motif content of each oligonucleotide.
6. (original) The method of claim 5 wherein relating the probability of antisense oligonucleotide activity to the motif content of each oligonucleotide is done by creation of a logistic regression model.
7. (original) The method of claim 5 further comprising selecting and eliminating motifs that are below a desired threshold of significance for probability of antisense oligonucleotide activity.
8. (original) The method of claim 7 wherein selecting and eliminating motifs that are below a desired threshold of significance for probability of antisense oligonucleotide activity is done using the likelihood ratio test.
9. (currently amended) A method of identifying an oligonucleotide sequence motif which ~~are~~ is predictive of antisense oligonucleotide activity comprising:
- ~~a. providing a set of antisense oligonucleotide sequences, each of which has an experimentally determined capacity to inhibit expression of its complementary nucleic acid target;~~
  - b. subdividing each ~~of said antisense oligonucleotide sequences~~ sequence of a set of antisense oligonucleotide sequences into subsequences from two to ten nucleotides in of defined length, each unique subsequence being a motif, wherein each of the antisense oligonucleotide sequences has an experimentally determined capacity to inhibit expression of its complementary nucleic acid target;
  - c. performing a T-test to determine ~~determining~~ which motifs significantly correlate with antisense oligonucleotide activity;
  - d. eliminating the motifs whose correlation with antisense oligonucleotide activity is unique to a particular nucleic acid target;

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e. creating a logistic regression model to relate ~~relating~~ the probability of antisense oligonucleotide activity to the motif content of each oligonucleotide; and

f. performing a likelihood ratio test to select and eliminate ~~selecting and eliminating~~ motifs that are below a desired threshold of significance for probability of antisense oligonucleotide ~~activity;~~ activity, wherein the remaining motifs are predictive of antisense oligonucleotide activity.

10. (canceled).

11. (currently amended) The method of ~~claim 10~~ claim 9 wherein the subsequences are ~~defined length of the motifs is~~ from three to four nucleotides in length.

12-16. (canceled).

17. (currently amended) A method of selecting an effective antisense oligonucleotide sequences ~~sequence~~ for inhibition of expression of a preselected target nucleic acid comprising:

~~providing a set of antisense oligonucleotide sequences of a selected length which are complementary to a preselected target nucleic acid sequence;~~

~~selecting the~~ an antisense oligonucleotide ~~sequences~~ sequence ~~in the set which contain~~ from a set of antisense oligonucleotide sequences, wherein the selected antisense oligonucleotide sequence comprises at least one activity-enhancing oligonucleotide sequence motif, and wherein the set of antisense oligonucleotide sequences are of a selected length which are complementary to a preselected target nucleic acid sequence.

18. (currently amended) The method of claim 17 further comprising selecting the an antisense oligonucleotide sequence ~~sequences identified in (b.)~~ which ~~do not contain~~ does not comprise an activity-decreasing oligonucleotide sequence motif.

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19. (currently amended) The method of claim 17 further comprising selecting the an antisense oligonucleotide sequence ~~sequences identified in (b.)~~ which ~~contain~~ comprises more than one activity-enhancing oligonucleotide sequence motif.

20. (currently amended) A method of selecting an effective antisense target ~~sequences~~ sequence for inhibition of expression of a preselected target nucleic acid comprising:

dividing a target nucleic acid sequence into a set of target sequence regions of a selected length for antisense targeting; and

selecting ~~the target~~ a target sequence regions region in the set which ~~contain~~ comprises at least one activity-enhancing target sequence motif.

21. (currently amended) The method of claim 20 further comprising selecting ~~the target a~~ target sequence region ~~regions identified in (b.)~~ which ~~do not contain~~ does not comprise an activity-decreasing target sequence motif.

22. (currently amended) The method of claim 20 further comprising selecting ~~the target a~~ target sequence region ~~regions identified in (b.)~~ which ~~contain~~ comprises more than one activity-enhancing target sequence motif.

23-24. (canceled).

25. (original) A method of designing an antisense oligonucleotide with enhanced likelihood of inhibiting expression of a preselected nucleic acid target comprising targeting said antisense oligonucleotide to a nucleic acid target sequence comprising one or more activity-enhancing target sequence motifs.

26. (original) The method of claim 25 wherein the target sequence does not contain an activity-decreasing target sequence motif.

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27. (original) The method of claim 25 wherein the target sequence comprises two or more activity enhancing motifs.

28. (original) A method of designing an antisense oligonucleotide with enhanced likelihood of inhibiting expression of a preselected nucleic acid target comprising targeting said antisense oligonucleotide to a nucleic acid target sequence which does not contain an activity-decreasing target sequence motif.

29. (original) The method of claim 28 wherein the target sequence contains one or more activity-enhancing target sequence motifs.

30-31. (canceled).